This invention relates to 3-alkyl-5-alkoxyethyleneoxazoles and to a method for their preparation and use. The compounds of this invention are represented by the formulas:

$$R_1\text{OCH}_2\text{CH}_2\text{N}_2\text{OCH}_2\text{R}_2$$

wherein $R_1$ and $R_2$ are alkyl groups of 1-4 carbon atoms, $n$ is an integer less than 3, and MS is a metal salt. These compounds have been unexpectedly found to exhibit many times the oral hypoglycemic activity of tolbutamide in standard test animals, such as rats. The pronounced activity of these 3,5-disubstituted oxazoles, coupled with their low order of toxicity, makes pharmaceutical compositions containing these compounds useful in reducing the blood sugar content of mammals, in particular for administration by the preferred oral route. Musante, Gazz. Chim. Ital. 68: 240 (1938), Chem. Centr., 1938, II (1405), discloses the reaction of 4-imino-5-methoxy-2-pentanone and hydroxylamine to give 5-methyl-3-methoxyethyleneoxazole and observes explicitly that the presently claimed 3-methyl-5-methoxymethyleneoxazole is not obtained because substitution of the imino group by the oxime radical occurs before ring formation. This reaction is as follows:

$$\text{NH}_2\text{OCH}_2\text{CH}_2\text{N}_2\text{OCH}_2\text{CH}_3 \rightarrow \text{NH}_2\text{OCH}_2\text{CH}_2\text{N}_2\text{OCH}_2\text{CH}_3$$

Musante also discloses the reaction of ethoxycacetlacete with hydroxylamine as giving 5-methyl-3-ethoxy-methyleneoxazole, as follows:

$$\text{CH}_3\text{OCH}_2\text{OCH}_2\text{C}_2\text{H}_5 + \text{NH}_2\text{OH} \rightarrow \text{CH}_3\text{OCH}_2\text{OCH}_2\text{C}_2\text{H}_5$$

It has now been unexpectedly found, however, that the reaction of, for example, methoxyacetacetone with hydroxylamine gives the 3-methyl-5-methoxymethoxazole (III) here claimed in isomeric mixture with I, above, according to the following:

$$\text{CH}_3\text{OCH}_2\text{OCH}_2\text{CH}_3 + \text{NE}_2\text{OH} \rightarrow \text{CH}_3\text{OCH}_2\text{OCH}_2\text{C}_2\text{H}_5$$

The desired 3-methyl-5-methoxymethoxazole (III) can then be obtained essentially free of I by separation from the mixture.

The method of this invention in the preparation of the novel compounds hereof thus comprises reaction between a 1-alkoxy-4-alkylbutane-2,4-dione, in which the alkyl groups contain 1-4 carbon atoms, and hydroxylamine to give an isomeric mixture of the corresponding 3-alkyl-5-alkoxyethyleneoxazoles and 5-alkyl-3-alkoxymethyleneoxazoles. This mixture is then separated to give the desired 3-alkyl-5-alkoxyethyleneoxazoles. The starting 1-alkoxy-4-alkylbutane-2,4-diones, such as methoxyacetacetone, ethoxycacetacetone, isopropoxycacetacetone and sec-butoxycacetacetone, are prepared by known methods from the appropriate ethylalkoxyacetate and alkylmethyketene in the presence of sodium ethoxide, according to the reaction:

$$R_1\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{R}_2 + \text{NaOH} \rightarrow \text{R}_1\text{OCH}_2\text{CH}_2\text{OCH}_2\text{R}_2$$

in which $R_1$ and $R_2$ are alkyl groups containing 1-4 carbon atoms.

In utilizing the compositions and practicing the method of this invention, the exact schedule of administration in animals is determined individually according to the subject's age, weight, response to the medication and nature and severity of the condition being treated. For use in reducing the blood sugar content, for example, from about 25 to about 500 mg of 3,5-disubstituted oxazole can be administered orally as a single dose one to four times daily.

In addition to 3-alkyl-5-alkoxyethyleneoxazoles as the sole active ingredient, other complementary ingredients can be included in the composition to secure advantageous combinations of properties especially adapted to individual situations in the treatment of the foregoing conditions. Thus, other hypoglycemic agents such as tolbutamide, chlorpropamide, phenformin hydrochloride, mesoxaline acid, insulin, nicotinic acid, and the like can be included in the present formulations in amounts not exceeding and preferably less than those normally employed in single unit doses where such added ingredients are employed alone. Utilizable potassium salts, such as potassium chloride, can be included to offset possible potassium losses during therapy.

Such combinations include also conventional therapeutic agents or compounds of or less of hypocholesterolmic agents such as the D-isomer of 3,5,5'-triodothyronine, triiodothyronine, propionic acid, and thyroxine-like compounds such as sodium L-thyroxine and sodium D-thyroxine glucocorticoids such as cortisone, prednisolone and 6a-methyl-prednisolone; anticoagulants such as heparin, 2-diphenylacetyl-1,3-lindanone, polyethylene sulfonate and dicumarol or its derivatives vitamins such as ascorbic acid, vitamin B12, ascorbic acid and pyridoxine hydrochloride; estrogens such as estradiol; androgens such as testosterone; combinations of estrogens and androgens such as estradiol and testosterone; unsaturated fatty acids or esters such as linoleic acid or esters; antibiotics such as neomycin; analogues such as aspirin; compounds associated with cholesterol synthesis or metabolism such as a-phenylbutyric acid and a-p-biphenylbutyric acid; lipotropic agents such as choline and inositol; amino acids such as asparagine and glycine; or other plant sterols; diuretics such as ethoxyazolamide and hydrochlorothiazide; anorexigenic agents such as amphetamine; cardiovascular agents (including vasodilators and hypotensive agents), such as chlorisondamine chloride, hexamethionum chloride, and penterythritol tetranitrate.

In adapting the active ingredients for use in mammals, the novel compositions are suitably presented for administration in unit dosage form as tablets, pills, capsules,
powders, wafers, cachets, granules, oral aqueous or oil dispersions, including elixirs, and the like. For preparing solid compositions such as tablets, the active ingredient is mixed with a conventional non-sugar tabletting component such as cornstarch, dicalcium phosphate, terra alba (calcium sulfate), talc, stearic acid, calcium stearate, gums and functionally similar materials constituting pharmaceutical diluents or carriers. The tablets or pills can be laminated or otherwise compounded to provide a dosage form affording the advantage of prolonged or delayed action or of predetermined successive action of the enclosed medication. For example, the tablet or pill can comprise an inner dosage and outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids or mixtures of polymeric acids with such materials as shellac, shellac and cetyl alcohol, cellulose acetate phthalate and the like. A particularly advantageous sustained release coating comprises a styrene maleic acid copolymer.

The liquid form in which the novel compositions of this invention can be incorporated are aqueous sugar-free solutions or suspensions, emulsions or suspensions with edible oils such as cottonseed oil, sesame oil, coconut oil, peanut oil and the like, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include the synthetic and natural gums such as tragacanth, acacia, dextran, methylcellulose, polyvinylpyrrolidone, gelatin and the like.

In preparing pharmaceutical compositions of 3-alkyl-5-alkoxyimethylisoxazole, the fact that certain of these compounds are water-insoluble, volatile liquids must be considered. Appropriate oral liquid dosage forms include conventional sugar-free syrups, elixirs and non-aqueous solutions for use as drops or by the teaspoonful. Suitable non-aqueous vehicles for oral use include the edible oils (e.g., peanut oil, cottonseed oil, coconut oil and other vegetable oils), mineral oil, glycerol, propylene glycol, polyethylene glycol, 200–600, sorbitol, ethanol, or mixtures of these (e.g., equal parts of peanut oil and propylene glycol). Aqueous vehicles include from about 1 to about 50% aqueous solutions of propylene glycol or ethanol or mixtures of the two comprising together the said percentages. Liquid preparations for intramuscular or subcutaneous injection can be prepared as ethanolic-aqueous or glycol-aqueous or oil solutions (e.g., vegetable oils such as peanut oil) and in repository-type vehicles such as aluminum monostearate-pasteurized oil gel. In general, liquid formulations range in concentration from about 0.5 to 20–40% 3-alkyl-5-alkoxyimethylisoxazole.

Solid dosage forms of liquid 3-alkyl-5-alkoxyimethylisoxazole, such as 3-methyl-5-methoxyimethylisoxazole, require the intermediate preparation of the liquid active ingredient as discrete solid particles which can be employed to build the ultimate dosage form by conventional methods. Alternatively, the liquid 3-alkyl-5-alkoxyimethylisoxazole can be dissolved or dispersed in an edible oil such as a vegetable or mineral oil (in ratios of oil to liquid, for example, about 1:1 to 1:200) and soft elastic capsules containing the oil dispersion or solution prepared for oral use. Triturates of the present compounds can be made using various absorbing powders such as kaolin, magnesium carbonate, bentonite, magnesium oxide, starch, calcium carbonate, tribasic calcium phosphate, magnesium trisilicate and the like. Emulsifying the liquid active ingredient, preferably dissolved in a suitable vegetable oil or mineral oil, to provide small particle sizes and then coating the said particles with a concentrate of one or more hydrophilic colloids, pharmaceutically acceptable copolymers, or mixtures thereof yields, on drying, free-flowing granulations which can be handled essentially as solid particles and formulated as powders, granules, tablets, hard-filled capsules and the like.

It has been found that a complex of a liquid 3-alkyl-5-alkoxyimethylisoxazole with a pharmaceutically acceptable metal salt of a crystalline solid which can be formulated on an equivalent weight basis into tablets, capsules, pills, powders, granules, pilules, and the like. Some metal salts are less desirable than others from the standpoint of toxicity and hygroscopicity, and the zinc salts, such as zinc chloride, zinc bromide, zinc phosphate, zinc sulfate, zinc nitrate, zinc acetate, zinc carbonate, and the like are preferred. However, the salt of other metals, such as iron, aluminum, magnesium and calcium, can also be used.

In preparing the metal salt complexes of 3-alkyl-5-alkoxyimethylisoxazole, such as 3-methyl-5-methoxyimethylisoxazole, the conventional procedures are employed to give complexes having either a 1:1 or 2:1 ratio of isoxazole to metal salt. The 2:1 complex, bis-3-alkyl-5-alkoxyimethylisoxazole, is preferred because it provides a higher proportion of isoxazole per unit weight of solid and is less hygroscopic. Bringing together the desired metal salt and the desired isoxazole in a common solvent, with stirring, is sufficient to produce the desired complex in high yield. A molar excess of isoxazole will give a 2:1 complex, less than a molar excess giving the 1:1 complex.

The term "unit dosage form" as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical diluent, carrier or vehicle. The specification for the novel unit dosage forms of this invention are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved and (b) the limitations inherent in the art of compounding such an active material for therapeutic use, as disclosed in detail in this specification, these being features of the present invention. Examples of suitable unit dosage forms, as herebefore described, are tablets, capsules, pills, powder pouches, wafers, cachets, granules, suspensions for oral or sterile injectable use, suppositories, and segregated multiples of any of the foregoing, and other forms alluded to herein.

The following examples illustrate the best mode contemplated for carrying out the invention, but such examples are not to be construed as limiting the scope thereof.

Example 1. 3-Methyl-5-methoxyimethylisoxazole

A stirred mixture of 26.0 g. of methoxycetyletone, 20.8 g. of hydroxymethylene hydrochloride and 20.8 g. of potassium carbonate was heated over an open bath at 130° C. for 4 hours. The mixture was allowed to cool and then was diluted with 75 ml. of water and extracted with ether. The ether extracts were dried over magnesium sulfate and concentrated. The residue was distilled at reduced pressure through a 6-inch Vigreux column to give 15.36 gm. (60.5%) of a colorless liquid boiling at 77–80° C. (12 mm.). Redistillation gave an analytical sample boiling at 78° C. (12 mm.).


The analytical sample above was further purified by vapor phase chromatography to give two distinct fractions. By nuclear magnetic resonance one fraction was identified as 3-methyl-5-methoxyimethylisoxazole and the other as 5-methyl-3-methoxyimethylisoxazole, each essentially free of the other isomer.
Example 2

Following the procedure of Example 1 but substituting equivalent amounts of other 1-alkoxy-4-alkylbutane-2,4-diones for the methoxyacetylaspetone therein, the alkyl group containing 1-4 carbon atoms, gives the corresponding 3-alkyl-5-alkoxymethylisoxazole, usually in isomeric mixture with the corresponding 5-alkyl-3-alkoxymethylisoxazole, from which the desired 3-alkyl isomer can be separated. By this method there is prepared, for example, 3 - methyl - 5 - ethoxymethylisoxazole, 3 - ethyl - 5 - isopropoxymethylisoxazole, 3 - methyl - 5 - secbutoxymethylisoxazole, 3 - ethyl - 5 - isopropoxymethylisoxazole, 3 - ethyl - 5 - sec - butoxymethylisoxazole and the corresponding 3-propyl- and 3-sec-butyl derivatives of the foregoing compounds.

Example 3.—Bis-3-methyl-5-methoxymethylisoxazole zinc chloride complex

A filtered solution of 203 gm. (1.49 moles) of zinc chloride in 2 liters of absolute ether is added over a 40-minute period to a filtered solution of 508 gm. (4.0 moles) of 3-methyl-5-methoxymethylisoxazole in 400 ml. of absolute ether. The mixture is stirred for 2½ hours and filtered to obtain a product which, on recrystallization from 1350 ml. of ethyl acetate, gives the zinc chloride complex of 3-methyl-5-methoxymethylisoxazole having a ratio of 2:1 3-methyl-5-methoxymethylisoxazole to zinc chloride (bis - 3 - methyl - 5 - methoxymethylisoxazole zinc chloride complex).

Example 4

Substituting other 3 - alkyl - 5 - alkoxymethylisoxazoles, such as those of Example 2, for the 3-methyl-5-methoxymethylisoxazole in the above reaction gives the corresponding zinc chloride complexes thereof.

Example 5

In foregoing Examples 3 and 4, other pharmaceutically acceptable metal salts can be substituted for the zinc chloride, the amounts being determined on a molar equivalent basis. In particular, other zinc salts, such as zinc bromide, zinc phosphate, zinc sulfate, zinc nitrate, zinc acetate, zinc carbonate and the like can be employed.

Example 6.—Soft gelatin capsules

A batch of 1,000 soft gelatin capsules, each containing 25 mg. of 3-methyl-5-methoxymethylisoxazole in mineral oil, is prepared from the following materials:

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-methyl-5-methoxymethylisoxazole</td>
<td>25 gm.</td>
</tr>
<tr>
<td>Mineral oil, U.S.P.</td>
<td>100 g.</td>
</tr>
</tbody>
</table>

A uniform dispersion of the active ingredient in the mineral oil is prepared and the dispersion filled into soft gelatin capsules by conventional means.

One capsule is given twice a day in the treatment of diabetes.

Example 7.—Non-aqueous preparation

One thousand milliliters of a non-aqueous liquid preparation containing 500 mg. of 3-methyl-5-methoxymethylisoxazole in each teaspoonful (5 ml.) is prepared by dispersing 100 gm. of active ingredient in a vehicle containing 600 ml. of peanut oil and propylene glycol, q.s. to 1000 ml.

Example 8.—Tablets

A lot of 100,000 compressed tablets, each containing 100 mg. of bis-3-methyl-5-methoxymethylisoxazole zinc chloride complex, is prepared from the following ingredients:

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bis-3-methyl-5-methoxymethylisoxazole zinc chloride complex</td>
<td>10,000 gm.</td>
</tr>
<tr>
<td>Terra alba (calcium sulfate)</td>
<td>25,000 gm.</td>
</tr>
<tr>
<td>Methycellulose, U.S.P. (15 cps.)</td>
<td>650 g.</td>
</tr>
<tr>
<td>Talc, bolted</td>
<td>4,500 g.</td>
</tr>
<tr>
<td>Calcium stearate, fine powder</td>
<td>350 g.</td>
</tr>
</tbody>
</table>

The complex and terra alba are mixed well, granulated with 7.5% solution of methycellulose in water, passed through a No. 8 screen and dried at 120° F. The dried granules are passed through a No. 12 screen, mixed thoroughly with the talc and stearate and compressed into tablets.

Substitution of other pharmaceutically acceptable zinc salt complexes for the above active ingredient, such as the bromide, phosphate, sulfate, nitrate, acetate, carbonate and the like, wherein the complex-metal salt ratio is 2:1, gives similarly utilizable tablets.

Example 9.—Capsules

A lot of 10,000 two-piece hard gelatin capsules for oral use, each containing 250 mg. of bis-3-methyl-5-methoxymethylisoxazole zinc chloride complex, is prepared from the following materials: Bis-3-methyl-5-methoxymethylisoxazole zinc chloride complex, 2500 gm.

The powdered bis-3-methyl-5-methoxymethylisoxazole zinc chloride complex is mixed with talc and starch and encapsulated in the usual manner.

One capsule is given once daily in the treatment of diabetes.

Example 10.—Oil suspension

An oil suspension for oral use, each 5 ml. containing 50 mg. of bis-3-methyl-5-methoxymethylisoxazole zinc chloride complex, is prepared from the following materials:

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saccharin sodium</td>
<td>0.5 gm.</td>
</tr>
<tr>
<td>Cyclamate sodium</td>
<td>0.1 gm.</td>
</tr>
<tr>
<td>Bis - 3 - methyl - 5 - methoxymethylisoxazole zinc chloride complex</td>
<td>100 gm.</td>
</tr>
<tr>
<td>Benzoic acid, powder</td>
<td>0.5 gm.</td>
</tr>
<tr>
<td>Methylparaben</td>
<td>0.5 gm.</td>
</tr>
<tr>
<td>Butylated hydroxyanisole</td>
<td>0.05 gm.</td>
</tr>
<tr>
<td>Oil of orange</td>
<td>1 ml.</td>
</tr>
<tr>
<td>Aluminum monostearate-corn oil gel</td>
<td>q.s. to 10,000 ml</td>
</tr>
</tbody>
</table>

One teaspoonful (5 ml.) is given twice daily in the treatment of diabetes.

Example 11

In each of foregoing Examples 6 through 10 the active ingredient can be replaced by other 3-alkyl-5-alkoxy methylisoxazoles and metal complexes thereof, such as those identified in Examples 2 through 5.

What is claimed is:

1. A therapeutic composition comprising: in dosage unit form, as the primary active ingredient, from about 25 to about 500 mg. of a compound selected from the group consisting of 3-methyl-5-methoxymethylisoxazole and 3-methyl-5-methoxymethylisoxazole zinc chloride complex, in combination with a pharmaceutical carrier.

2. A method for reducing the blood sugar content of mammals comprising: administering to a mammal a 3-alkyl-5-alkoxymethylisoxazole selected from the group consisting of compounds of the formula:

```
    R2OCH2
    R1
    R3
```

and

```
    R2OCH2
    R1
    R4
```

and

```
    R2OCH2
    R1
    R5
```

and
wherein $R_1$ and $R_2$ are alkyl groups of 1–4 carbon atoms, $n$ is an integer less than 3, and $MS$ is a pharmaceutically acceptable metal salt.

3. A method for reducing the blood sugar content of mammals comprising: administering to a mammal a compound selected from the group consisting of 3-methyl-5-methoxymethylisoxazole and 3-methyl-5-methoxymethylisoxazole zinc chloride complex.

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